Amendments to the Claims

Please cancel claims 46-65.

1. (Original) A method of treating a disease or disorder characterized by high intracellular calcium levels in an individual in need thereof, comprising:

providing an effective amount of an opener of maxi-K potassium channels to said individual, wherein said opener activates maxi-K potassium channels in cells under conditions of high intracellular calcium concentration, and does not significantly activate maxi-K potassium channels in cells under low or normal concentrations of intracellular calcium.

2. (Original) The method according to claim 1, further wherein influx or introduction of additional calcium into cells having high intracellular calcium concentration is restricted or reduced.

3. (Original) The method according to claim 1, wherein the disease or disorder is a neurodegenerative disease or disorder.

4. (Original) The method according to claim 3, wherein the neurodegenerative disease or disorder is selected from the group consisting of stroke, global cerebral ischemia, traumatic brain injury, Parkinson's disease, epilepsy, migraine and Alzheimer's disease.

5. (Original) The method according to claim 4, wherein the neurodegenerative disease is stroke.

6. (Original) The method according to claim 5, wherein the neurodegenerative disease is ischemic stroke or acute ischemic stroke.

7. (Original) The method according to claim 6, wherein the cells having a high intracellular calcium concentration are preischemic or ischemic neurons.

8. (Original) The method according to claim 1, wherein the maxi-K potassium channel opener is selected from the group consisting of fluoro-oxindole compounds and chloro-

oxindole compounds.

9. (Original) The method according to claim 8, wherein the fluoro-oxindole compound is selected from the group consisting of (±)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one; and (3S)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

10. (Original) The method according to claim 9, wherein the fluoro-oxindole compound is (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluero-6-(trifluoromethyl)-2H-indole-2-one.

11. (Original) The method according to claim 8, wherein the chloro-oxindole compound is selected from the group consisting of (±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; and (3R)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one.

12. (Original) The method according to claim 1, wherein the maxi-K potassium channel opener is administered prior to or following the onset of the disease or disorder.

13. (Original) The method according to claim 5 or claim 6, wherein the maxi-K potassium channel opener is administered prior to or following the onset of stroke, ischemic stroke, or acute ischemic stroke.

14. (Original) A method of treating stroke in an individual in need thereof, comprising:

administering to the individual an effective amount of a maxi-K channel opener, said opener having opener activity on maxi-K potassium channel proteins in neuronal cells having a high intracellular calcium concentration, while having no significant opener activity on maxi-K potassium channel proteins in neuronal cells having normal or low intracellular calcium concentration.

15. (Original) The method according to claim 14, wherein the maxi-K channel opener is selected from the group consisting of fluoro-oxindole compounds and chloro-oxindole compounds.

16. (Original) The method according to claim 15, wherein the fluoro-oxindole compound is selected from the group consisting of (±)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one; and (3S)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

17. (Original) The method according to claim 16, wherein the fluoro-oxindole compound is (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

18. (Original) The method according to claim 15, wherein the chloro-oxindole compound is selected from the group consisting of (±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; and (3R)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one.

19. (Original) The method according to claim 14, wherein ischemic stroke or acute ischemic stroke is treated.

20. (Original) The method according to claim 14 or claim 19, wherein the maxi-K channel opener is administered prior to or following the onset of stroke, ischemic stroke or acute ischemic stroke.

21. (Original) The method according to claim 14, wherein the maxi-K channel opener provides cortical neuroprotection by restricting entry of calcium into neuronal cells exposed to toxic levels of calcium.

22. (Original) A method of treating a disease or disorder characterized by high

intracellular calcium levels in an individual in need thereof, comprising:

a) providing to the individual an opener of maxi-K channels wherein the opener is sensitive to high intracellular calcium concentration and targets maxi-K channels in cells associated with the disease or disorder and having high intracellular calcium concentration, while not significantly targeting cells having low or normal intracellular calcium concentration; and

b) reducing or restricting influx of additional calcium into the cells associated with the disease or disorder, increasing potassium efflux and regulating membrane potential, thereby protecting the cells associated with the disease or disorder from toxicity or death.

23. (Original) The method according to claim 22, wherein the maxi-K channel opener is a fluoro-oxindole compound or a chloro-oxindole compound.

24. (Original) The method according to claim 23, wherein the fluoro-oxindole compound is selected from the group consisting of (±)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one; and (3S)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

25. (Original) The method according to claim 24, wherein the fluoro-oxindole compound is (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

26. (Original) The method according to claim 24, wherein the fluoro-oxindole compound is (3S)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

27. (Original) The method according to claim 23, wherein the chloro-oxindole compound is selected from the group consisting of (±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; and (3R)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one.

28. (Original) The method according to claim 22, wherein the disease or disorder is a neurodegenerative disease or disorder.

29. (Original) The method according to claim 28, wherein the neurodegenerative disease or disorder is selected from the group consisting of stroke, global cerebral ischemia, traumatic brain injury, Parkinson's disease, epilepsy, migraine and Alzheimer's disease.

30. (Original) The method according to claim 29, wherein the neurodegenerative disease or disorder is stroke.

31. (Original) The method according to claim 30, wherein the neurodegenerative disease or disorder is ischemic stroke or acute ischemic stroke.

32. (Original) The method according to claim 22, wherein the cells associated with the disease or disorder and having a high intracellular calcium concentration are at-risk preischemic neurons or ischemic neurons.

33. (Original) The method according to claim 29, wherein the neurodegenerative disease or disorder is traumatic brain injury.

34. (Original) The method according to claim 22, wherein the maxi-K channel opener is administered prior to or after the onset of the disease or disorder.

35. (Original) A method of providing neuroprotection from stroke in an individual in need thereof, comprising: administering an effective amount of a maxi-K potassium channel opener compound that activates maxi-K potassium channel proteins in neurons having a high intracellular calcium concentration, while having no significant opener activity on maxi-K potassium channel proteins in neurons having low or normal intracellular calcium concentration.

36. (Original) A method of providing neuroprotection from stroke in an individual in need thereof, comprising: administering an effective amount of a fluoro-oxindole or chloro-oxindole compound to the individual wherein the compound is a maxi-K potassium channel opener compound

that activates maxi-K potassium channel proteins in neurons having a high intracellular calcium concentration, while having no significant opener activity on maxi-K potassium channel proteins in neurons having low or normal intracellular calcium concentration, thereby providing cortical neuroprotection by restricting entry of calcium into the neurons at risk for neurotoxicity or death.

37. (Original) The method according to claim 35 or claim 36, wherein the maxi-K channel opener compound is a fluoro-oxindole compound.

38. (Original) The method according to claim 37, wherein the fluoro-oxindole compound is selected from the group consisting of (±)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one; and (3S)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

39. (Original) The method according to claim 38, wherein the fluoro-oxindole compound is (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

40. (Original) The method according to claim 38, wherein the fluoro-oxindole compound is (3S)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indole-2-one.

41. (Original) The method according to claim 35 or claim 36, wherein the maxi-K channel opener compound is a chloro-oxindole compound.

42. (Original) The method according to claim 41, wherein the chloro-oxindole compound is selected from the group consisting of (±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one; and (3R)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-chloro-6-(trifluoromethyl)-2H-indol-2-one.

43. (Original) The method according to claim 35 or claim 36, wherein the maxi-K

channel opener compound is administered prior to or after the onset of stroke.

44. (Original) The method according to claim 35 or claim 36, wherein the neuroprotection is for ischemic stroke or acute ischemic stroke.

45. (Original) The method according to claim 35 or claim 36, wherein the neurons having high intracellular calcium concentration are preischemic and/or ischemic neurons.

46-65. (Canceled)

I. Status of the Claims

Claims 1-65 are pending. Claims 46-65 have been withdrawn. Claims 1-45 have been examined.

Claims 1-10, 12-17, 19-26, 28-40 and 43-45 stand rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,565,483 to Hewawasam and U.S. Patent No. 5,602,169 to Hewawasam.

Claims 1-45 stand rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,565,483 to Hewawasam and U.S. Patent No. 5,602,169 to Hewawasam.

II. Response to the Restriction Requirement

The Patent Office withdrew claims 46-65 from consideration as drawn to non-elected inventions. Accordingly, applicants have canceled claims 46-65. Applicants hereby reserve the right to file one or more subsequent applications directed to the subject matter of claims 46-65.

III. Response to the Rejection of Claims 1-10, 12-17, 19-26, 28-40 and 43-45 Under 35 U.S.C. §102(b)

The Patent Office rejected claims 1-10, 12-17, 19-26, 28-40 and 43-45 under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 5,565,483 to Hewawasam and U.S. Patent No. 5,602,169 to Hewawasam. The Patent Office states the '483 patent teaches "Example 14 (column 25) that is an opener of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and is useful in the treating of disorders (e.g., ischemic stroked, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels." Office Action, page 4. The Patent Office states the '169 patent teaches "Example 14 (column 26), Example 37 (column 31), and Example 38 (column 31) which are openers of the large-conductance calcium-activated potassium channels and are useful in the treating of disorders (e.g., ischemic stroked, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels." Office Action, page 4. Applicants respectfully traverse the rejection and submit the following comments.

As applicants argued previously, the '483 and '169 patents are generally directed to novel substituted 3-phenyl oxindole derivatives that are modulators of maxi-K channels. Neither the '483 nor the '169 patent teach methods of treatment or compounds which selectively open maxi-K channels disposed in neuronal cells having high intracellular calcium levels (e.g., traumatized cells), while not opening maxi-K channels disposed in neuronal cells having a normal physiological

calcium concentration. That is, neither of the cited references teach that a compound can be employed in a therapeutic capacity by selectively and preferentially opening maxi-K channels in neuronal cells having a high intracellular calcium concentration, while simultaneously NOT opening maxi-K channels in neuronal cells having a normal physiological intracellular calcium concentration.

Normal, healthy, non-traumatized neuronal cells have a physiological level of intracellular calcium. When neuronal cells are stressed, however, intracellular calcium concentrations are elevated above normal physiological levels. These high intracellular calcium levels can arise when neuronal cells are subjected to various forms of trauma, such as neurotoxic aspects that accompany stroke, particularly ischemic stroke, and neurodegenerative conditions. In one aspect, the methods of the present invention provide a heretofore unknown method of protecting neuronal cells that may be at risk during stroke or other neural trauma event.

Applicants respectfully submit that it appears that the Patent Office has misconstrued applicants' invention. Applicants' reading of the Office Action suggests that the Patent Office's anticipation rejections are premised on the belief that applicants are claiming the actual channel openers themselves, which is not the case. In the present case, applicants are claiming various methods in which neuronal cells are selectively targeted for maxi-K channel opening based on intracellular calcium concentration. In the methods of the present invention, neuronal cells in which intracellular calcium levels are elevated relative to normal physiological levels are targeted selectively. As the data presented in the Specification indicates, neuronal cells that express maxi-K channels, but do not have elevated intracellular calcium levels, are not targeted by the compounds used as exemplary compounds in the Laboratory Examples. The methods claimed in the subject patent application are directed to this discovery; the particular openers themselves are not being claimed.

Bearing the above comments in mind, applicants respectfully submit that the cited references, the '169 and '483 patents, do not anticipate the claims because they do not disclose each and every element of the claimed invention. Specifically, the cited references do not disclose the selective opening of maxi-K channels present in neuronal cells having intracellular calcium concentrations that are higher than normal physiological intracellular calcium levels. As noted, applicants are not claiming the openers themselves; rather applicants are claiming methods of treating conditions wherein a maxi-K channel opener is employed to open only those channels that are present in neuronal cells in which high intracellular calcium conditions are present.

Summarily, applicants submit that the cited references, do not anticipate the claimed invention because these references do not disclose each and every aspect of the claimed invention. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §102(b) be reconsidered and withdrawn in light of the above remarks.

IV. Response to the Rejection of the Claims Under 35 U.S.C. §103(a)

The Patent Office rejected claims 1-45 under 35 U.S.C. §103(a) as obvious over the '483 and '169 patents. Summarily, it is the Patent Office's position that the cited references "teach fluoro-oxindole compounds, which are openers of the large-conductance calcium–activated potassium channels (also known as maxi-K channels) and are useful in the treating of disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels." Office Action, page 6. Applicants respectfully traverse the rejection and submit the following comments.

Applicants respectfully reiterate the above remarks and those presented previously in prosecution. Applicants' invention is generally directed to the observation that neuronal cells having high intracellular calcium concentrations can be specifically targeted. This aspect of the presently claimed invention is absent from the cited references. In formulating its rejection of the claims under 35 U.S.C. §103(a), it appears that the Patent Office has maintained its focus on the identity of the compounds presented in the cited references and compared those compounds to the compounds employed in the Laboratory Examples of the present invention, which the Patent Office believes are being claimed. For example, the Patent Office states, "The different between some of the products taught by the Hewawasam et al. references and the products instantly claimed is that of generic description (e.g., see instant claim 8). The difference between some of the products taught by the Hewawasam et al. references and the products instantly claimed (e.g., see instant claim 11) is that of fluoro-oxindole instead of chloro-oxindole." Office Action, page 6.

Continuing, the Patent Office presents a discussion of Ex parte Wiseman, explaining that the "the different between the claimed compounds and the compounds of the prior art is two fluorine atoms versus chlorine atoms." Office Action, page 7. Applicants again take this discussion to indicate that the Patent Office is focusing its analysis and rejection of the claims on the belief that applicants are claiming the particular maxi-K openers presented in the Laboratory Examples. This is not the case; applicants' present patent applications does not feature a single claim directed to a specific compound.

Applicants reiterate that no such compounds are being claimed, per se, in the subject patent application. The claims of the present are directed to various methods, for example a method of treating a disease or disorder characterized by high intracellular calcium levels. Indeed, the preamble of claims 8 and 11, which were identified by the Patent Office, recite "The *method* according to claim 1" and "The method according to claim 8," respectively. Thus, contrary to the Patent Office's analysis, there are no "products instantly claimed." Applicants further respectfully note that terminal disclaimers over the '169 and '483 patents are already of record in the present case.

In order for the Patent Office's rejection of the claims under 35 U.S.C. §103(a) to stand, the cited references must disclose each and every element of the claimed invention, present a suggestion to modify the cited references to arrive at the claimed invention and there must be a reasonable chance of successfully making the combination, which are the elements of a *prima facie* case of obviousness. Applicants respectfully submit that the Patent Office has not met its burden.

The cited references do not disclose every element of the claimed invention. For example, the cited references do not disclose the ability to selectively open maxi-K channels situated in neuronal cells having an elevated intracellular calcium concentration, while not opening maxi-K channels situated in neuronal cells having normal physiological levels of calcium. This element is found in each of claims 1-45, directly or indirectly, but is absent from the cited references. As such, the cited references do not disclose each and every element of the claimed invention and do not meet the first prong of the *prima facie* case of obviousness.

Turning next to the suggestion or motivation prong of the *prima facie* case, no such suggestion is found in the cited references. As applicants have argued herein, the cited references are generally directed to compounds, but do not disclose or suggest the element of selective targeting of neuronal cells having high intracellular calcium levels to the exclusion of neuronal cells having physiological intracellular calcium levels. Taken in its proper context, the question of whether an explicit or implicit suggestion is found in the cited references then becomes a question of whether the cited references suggest the selective effect of a compound on neuronal cells expressing maxi-K channels and having high intracellular calcium levels, such as traumatized neuronal cells, to the exclusion of neuronal cells that also express maxi-K channels but do not have elevated levels of intracellular calcium. In this regard, the cited references make no such suggestion nor do they offer any motivation.

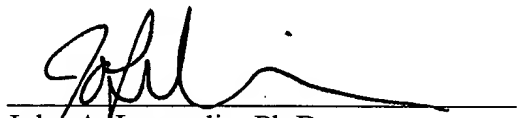
In view of the above, applicants respectfully submit that the Patent Office has not made out a *prima facie* case of obviousness. Applicants submit that the cited references do not disclose each and every element of the claimed invention, nor do the cited references offer any explicit or implicit suggestion or motivation. Accordingly, applicants respectfully request that the rejection of claims 1-45 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

V. Conclusions

In consideration of the above amendments and remarks, applicants respectfully request that the rejections of record be reconsidered and withdrawn. Applicants further submit that the subject patent application is in condition for allowance and courteously solicits a Notice of Allowance.

Although it is believed no additional fee is due, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment associated with the filing of this correspondence to Deposit Account Number 19-3880. Furthermore, if any extension of time is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to Deposit Account Number 19-3880.

Respectfully submitted,



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